

Drug Metabolizing Enzyme Activity of In Vitro Human Dermal (EpiDerm™) and Airway (EpiAirway™) Epithelial Models: Relationship to Genotoxicity of Chemicals as Determined by In Vitro Skin Micronucleus Assays.

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Purpose: Human dermal and airway epithelia contain xenobiotic metabolizing enzymes (XME) that could cause biotransformation of cosmetic ingredients, hair-dyes and other chemicals into toxic/mutagenic metabolites. The present work evaluated functional expression of XMEs in highly differentiated in vitro models of human dermal (EpiDerm™) and airway (EpiAirway™) epithelia.

Methods: RT-PCR and quantitative real-time PCR array experiments were conducted to analyze expression of 168 Phase I and Phase II XMEs in the models. To evaluate the functional activity of XMEs, an in vitro skin micronucleus assay was also performed with genotoxic chemicals known to require metabolic activation.

Results: Phase I enzymes found to be expressed in the models include cytochrome P450 (CYP) isoforms, alcohol dehydrogenases, aldehyde dehydrogenases, monoamine oxidases, flavin-containing monooxygenases and others. Further expression of some enzymes could be induced by 3-Methylcholanthrene (3MC). Phase II enzymes found to be expressed included glutathione S-transferases, glucuronosyl transferases, sulfotransferases, N-acetyl transferases, epoxidases, esterases, and others. In vitro skin micronucleus assays conducted on EpiDerm™ tissues topically treated with genotoxins confirmed metabolic activation of 4 chemicals that are known to require metabolic activation in order to produce genotoxicity. These results show that the EpiDerm™ and EpiAirway™ in vitro human skin and airway epithelial models possess functional drug metabolizing activity that can result in biotransformation of chemicals and generation of genotoxicity as determined by an in vitro skin micronucleus assay. These models and assays should prove useful for in vitro genotoxicity testing of cosmetic formulations as well as in vitro testing of chemicals for the REACH program.

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